REMARKS

Claims 1-7 are pending in this application. Claims 3-7 have been withdrawn from consideration. Claims 1 and 2 have been rejected. Claims 2-7 have been canceled. Claim 1 has been amended. Reconsideration is respectfully requested in light of the following remarks.

I. Election/Restriction

The Restriction Requirement placing claims 1 and 2 in Group I and claims 3-7 in Group II has been deemed proper and made Final. Accordingly, Applicants have canceled claims 3-7 without prejudice, reserving the right to file continuing applications on the canceled subject matter.

II. Rejection of Claims Under 35 U.S.C. 102(b)

Claims 1 and 2 have been rejected under 35 U.S.C. 102(b) as being anticipated by Geyer et al. (1988). The Examiner suggests that his reference teaches administration of methotrexate to adult rats before irradiating the spinal cord to protect against white matter necrosis and paralysis. Applicants respectfully disagree with the Examiner's conclusions regarding this reference.

Geyer et al. (1988) discloses the use of methotrexate to protect against neurotoxicity, specifically white matter necrosis, during radiation treatment. In the paper the authors report that methotrexate treatment, only when given before radiation therapy, is able to protect the animal from the white matter necrosis in the cervical spinal cord area, an effect that occurs following radiation treatment in this animal model. Nowhere in this paper do the authors suggest or even mention the use of methotrexate as claimed for prevention or reduction of pain. In fact, the white matter necrosis seen in this model is not a pain model but leads to paralysis, a condition that is associated with no sensations in the limbs at all and has not been described as a pain model. In fact, in the specification as filed, it is taught that the pain to be treated by methotrexate administration is pain induced not by tissue necrosis at all but by herniation of a disc and induction of an inflammatory response. Therefore, nowhere does the paper of Geyer et al. (1988) teach or suggest such an effect as is taught in the specification as filed and claimed in claims 1 and 2 as filed, claims that are limited to prevention and reduction of pain in an animal or prevention or reduction of lower back pain with radiculopathy.

In order to anticipate an invention the cited reference must tech each and every limitation of the claims (MPEP 2131). Accordingly, this reference cannot anticipate the instant invention of claims 1 and 2 because it fails to teach either prevention or reduction of pain with use of methotrexate. Withdrawal of this rejection is therefore respectfully requested.

Claim 1 has been rejected under 35 U.S.C. 102(b) as being anticipated by Mori et al. (1996). The Examiner suggests that this paper discloses administration of methotrexate to animals and that the drug produced an analgesic effect with regard to pain induced by acetic acid induced writhing in mice. Applicants respectfully traverse this rejection.

At the outset, Applicants have amended the claims to include the limitations of claim 2 in independent claim 1, where claim 1 comprises a method of preventing and reducing lower back pain with radiculopathy. Support for this amendment to the claims can be found throughout the specification as filed.

Mori et al. (1996) is a Japanese paper that was available to the Examiner and the Applicants in English only as an abstract. In this abstract, the authors report that at doses of 3 mg/kg and greater (orally) of methotrexate, the drug had a "weak analgesic effect" to reduce acetic acid-induced writhing in mice. The

abstract also reports that methotrexate had no analgesic effects at doses up to 30 mg/kg when the pain was induced by thermal stimuli. Therefore, this paper at best, supports the analgesic activity of methotrexate only at specific doses and only in response to specific types of pain. The paper teaches that the analgesic effects of the drug are limited at best. Nowhere does this paper teach or suggest that methotrexate is capable of preventing or reducing lower back pain with radiculopathy as now claimed. In order to anticipate an invention the cited reference must teach each and every limitation of the claims (MPEP 2131). Accordingly, this reference cannot anticipate the instant invention of claims 1 and 2 because it fails to teach either prevention or reduction of lower back pain with radiculopathy by administering methotrexate. Withdrawal of this rejection is therefore respectfully requested.

II. Rejection of Claims Under 35 U.S.C. 103(a)

Claim 2 has been rejected under 35 U.S.C. 103(a) as being unpatentable over Mori et al. (1996). The Examiner suggests it would have been *prima facie* obvious for one of ordinary skill in the art to administer methotrexate for pain relief since Mori et al. teach pain relief when this drug is used in mice. Applicants respectfully traverse this rejection.

As discussed *supra*, the authors report that only at doses of 3 mg/kg and greater (orally) of methotrexate, the drug had a "weak analgesic effect" to reduce acetic acid-induced writhing in mice. The abstract also reports that methotrexate had no analgesic effects at doses up to 30 mg/kg when the pain was induced by thermal stimuli. Therefore, this paper at best, supports the analgesic activity of methotrexate only at specific doses and only in response to specific types of pain. The paper teaches that the analgesic effects of the drug are limited at best. Nowhere does this paper teach or suggest that methotrexate is capable of preventing or reducing lower back pain with radiculopathy as now claimed.

To establish a *prima facie* case of obviousness, three basic criteria must be met. MPEP 2143. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art must teach or suggest all claim limitations. The fact that the teachings of Mori et al. are mixed in terms of the type of pain involved would not allow one of skill in the art to understand and expect that lower back pain with radiculopathy

could be successfully treated. Accordingly, this paper cannot make obvious the instant invention which is limited to a specific type of pain response. However, in an earnest effort to advance the prosecution, Applicants have further amended claim 1 to specify that the dose of methotrexate administered is 1 mg/kg or less. Support for this amendment to the claims can be found at page 8 of the specification as filed. Based on this further amendment to claim 1, the paper of Mori et al. (1996) also fails to teach the limitations of the claims. Accordingly, this paper cannot establish a *prima facie* case of obviousness and withdrawal of this rejection is respectfully requested.

IV. Conclusion

Applicants believe that the foregoing comprises a full and complete response to the Office Action of record. Accordingly,

favorable reconsideration and subsequent allowance of the pending claims is earnestly solicited.

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